Quantitative Predictions of Tautomeric Equilibria for 2-, 3-, and 4-Substituted Pyridines in both the Gas Phase and Aqueous Solution: Combination of AM1 with Reaction Field Theory

Mati M. Karelson,*[,‡] Alan R. Katritzky,*[,§] Miroslaw Szafran,[§,⊥] and Michael C. Zerner*[,‡]

Laboratory of Chemical Kinetics and Catalysis, Tartu State University, Kingissepa St. 16, 202400 Tartu, Estonian S.S.R., U.S.S.R., and Department of Chemistry, University of Florida, Gainesville, Florida 32611

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The AM1 method gives results in quantitative agreement with experimentally determined K_T values for 2-hydroxy- and 2-mercaptopyridine in the gas phase, and appears to be satisfactory for the general treatment of prototropic equilibria. Combination of the AM1 method with inclusion of the solvent reaction field leads to good quantitative agreement with K_T values determined experimentally in aqueous solution.

Introduction

Tautomeric phenomena in general, and the tautomerism of heterocycles in particular, are of great importance in many areas of chemistry and biochemistry. Extensive experimental and theoretical studies of such tautomeric equilibria have been reviewed.[1-5] Some of the most extensively studied equilibria are the tautomerism of various 2-, 3-, and 4-substituted pyridines. A recent paper,[6] from one of our laboratories found that the AM1 method reproduced correctly the relative stabilities and proton affinities for hydroxy- and thiopyridines in the gas phase. The present paper extends these AM1 calculations to consider the condensed phase. The corresponding experimental equilibrium constants are readily available for most of the hydroxy-, amino-, thioxo-, and methylpyridines in dilute aqueous solution.[8] Tautomerization energies alter on change of environment, and a study of such variations gives insight into the influence of, for example, solvent effects on molecular stability.

The total interaction energy, ΔE, can be divided into separate and additive terms as shown in eq 1, where E_{es}

$$\Delta E = E_{es} + E_{pol} + E_{disp} + E_{ex} + E_{ct} + E_{corr} \quad (1)$$

is the electrostatic interaction, E_{pol} the polarization interaction, E_{disp} the dispersion energy, E_{ex} the exchange repulsion, E_{ct} the charge transfer or electron delocalization interaction, and E_{corr} the electron-correlation energy. This model has been applied to both weak and strong complexes, to hydrogen bonded and charge transfer complexes, to the solvation of ions, to proton affinities in aqueous solution, to proton-transfer reactions in solution, and to hydrated electrons.[9] However, such applications are presently restricted to small molecules because of computing time requirements. Most molecules of present interest in chemistry and biochemistry require simplifying assumptions to make the problem tractable.

Modern theories of solvent effects on molecular complexes distinguish two types of interaction: (i) nonspecific or physical and (ii) specific or chemical.[10] Physical interactions with the solvent are arbitrarily divided into dispersion and electrostatic solvation; the latter can be described on the basis of a reaction field model introduced by Onsager.[11] Examples of the results of chemical interactions are hydrogen bonding, charge transfer complexes, and dipole–dipole complexes (observed for molecules with $\mu > 4$ D).

Several authors[12-15] have noticed that the polarity of the medium is most important in determining the solvent influence on tautomeric equilibria. A self-consistent reaction field (SCRF) method was proposed elsewhere[11] to include this effect in theoretical calculations. The results of AM1 SCRF quantum-chemical investigations of the tautomeric equilibria of various five-membered heterocycles with two heteroatoms show[16] that the introduction of the solvent reaction field into the Hamiltonian of the isolated molecule gives qualitatively correct relative stabilities for the different tautomers of the same heterocycle in solution.

The electrostatic solvation effect can be treated as a perturbation H^1 to the Hamiltonian of the isolated molecule, H_o.[11d]

$$H = H_o + H^1 \quad (2)$$

‡ Tartu State University.
§ University of Florida.
⊥ On leave from Department of Chemistry, A. Mickiewicz University, 60780 Poznan, Poland.

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Table I. Calculated AM1 Heats of Formation ΔH_f (kcal/mol) for the Tautomeric Forms of Various Substituted Pyridines and Comparison of the Corresponding Tautomeric Equilibrium Constants with Experimental Values

	heterocycle	index	ΔH_f, kcal/mol		log K_T (calc)		log K_T (exp)[8a]
			$\epsilon = 1$	$\epsilon = 78.4$	$\epsilon = 1$	$\epsilon = 78.4$	$\epsilon = 78.4$
1.	2-hydroxypyridine	I	-11.79	-12.30			
2.	2-pyridone	II	-11.24	-16.09	0.4	-2.8	-3.1
3.	2-aminopyridine	III	35.86	35.44			
4.	2-iminopyridine	IV	49.24	46.13	9.8	7.8	6.0
5.	2-mercaptopyridone	V	39.61	38.77			
6.	2-thioxopyridone	VI	41.97	32.39	1.7	-4.7	-4.7
7.	2-methylpyridine	VII	25.67	24.89			
8.	2-methylenepyridine	VIII	45.85	45.05	14.8	14.8	13.3
9.	3-hydroxypyridine	IX	-11.50	-14.80			
10.	3-pyridone	X	7.89	-4.94	14.3	6.7	0.1
11.	3-aminopyridine	XI	34.11	31.60			
12.	3-iminopyridine	XII	64.73	58.76	22.5	20.0	*a*
13.	3-mercaptopyridine	XIII	40.48	38.2			
14.	3-thioxopyridine	XIV	58.88	34.92	13.5	-2.4	-2.2
15.	3-methylpyridine	XV	24.13	22.92			
16.	3-methylenepyridine	XVI	61.81	57.85	27.7	25.7	*a*
17.	4-hydroxypyridine	XVII	-12.33	-13.59			
18.	4-pyridone	XVIII	-4.20	-17.68	6.0	-3.0	-3.3
19.	4-aminopyridine	XIX	34.24	32.99			
20.	4-iminopyridine	XX	49.89	42.76	11.5	7.2	8.7
21.	4-mercaptopyridine	XXI	40.20	39.59			
22.	4-thioxopyridone	XXII	49.02	29.66	6.5	-7.3	-4.6
23.	4-methylpyridine	XXIII	24.19	22.76			
24.	4-methylenepyridine	XXIV	45.90	42.89	16.0	14.8	13.4

[a] XH form strongly predominating.

The perturbation may be quite conveniently described by the reaction field model introduced by Onsager.[11a] The charge density anisotropy, as revealed by its dipole moment M, plays the central role. This dipole polarizes the surroundings, and this new field reacts back on the solute (molecular) system. Solving this problem[11a] creates an image dipole in the solvent proportional to the solute dipole itself:

$$\underline{R} = gM \tag{3a}$$

where $\underline{M} = \langle\Psi|\underline{\mu}|\Psi\rangle$; with $\underline{\mu}$ the total dipole operator, and $\underline{R}$ the image dipole, or reaction field. The structure of g depends on the assumptions of the solvent reaction. Following Onsager[11a] and Tapia and Goscinski,[11e] we use:

$$g = \frac{2(\epsilon - 1)}{r_c^3(2\epsilon + 1)} \tag{3b}$$

where ϵ is the bulk dielectric constant and r_c is the cavity radius. The interaction of the solute molecule with the field is then given by:

$$H^1 = -\underline{\mu}\cdot\underline{R} \tag{4}$$

The electronic energy of a solute molecule in the dielectric medium is calculated by solving the respective one-electron Fock equations. These equations are obtained by varying the total energy $\langle\Psi'|H|\Psi'\rangle$ with respect to the trial wave function Ψ', subject to the usual orthonormality constraints and the additional Lagrange constraint $\gamma[\langle\Psi'|\underline{m}|\Psi'\rangle g\langle\Psi'|\underline{m}|\Psi'\rangle - g\underline{M}^2]/2$. The resulting Fock equation is:

$$[f_o - \underline{\mu}\cdot\underline{R}]\phi_i = \epsilon_i\phi_i \tag{5}$$

with ϕ_i the molecular orbital of energy ϵ_i in the reaction field.

Equation 5 is a nonlinear equation: both f_o and $\underline{R}$ depend on the orbitals ϕ_i. $\underline{R}$ depends on $\underline{M}$ through eq 3. $\underline{M}$ in turn depends on the wave function Ψ', which in turn is a product of molecular orbitals obtained through solving eq 5. In practice it takes very little additional effort to solve these equations iteratively for $\underline{R}$ and f_o than it does for f_o itself. Solving these equations self-consistently, however, allows the inclusion of higher order effects. The total energy of the solute, E, is given by:

$$E = \langle\Psi|H|\Psi\rangle = \langle\Psi|H_o|\Psi\rangle - \underline{MR} \tag{6a}$$

If we now include the polarization energy of the solvent,

$$E_{tot} = E + \tfrac{1}{2}\underline{MR} = \langle\Psi|H_o|\Psi\rangle - \tfrac{1}{2}\underline{MR} \tag{6b}$$

The MOPAC program package[17] was modified by including $-\underline{\mu R}$ with f_o and made to solve eq 5. No other modifications are required.

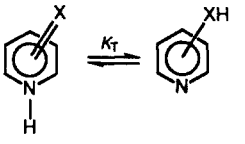
The choice of an appropriate cavity radius, r_c, is a subject of much discussion.[10,11h] In this paper we used a simple relation between r_c and molecular volume, V_c (eq 7), where N_a is Avogadros' number.

$$(r_c)^3 = 3V_c/(4\pi N_a) \tag{7}$$

Some attempts were also undertaken to adopt the Onsager model for an ellipsoidal cavity and to higher order moments.[10,11c,11g] In most cases, however, these modifications do not essentially influence the results. These approaches lead to more complicated calculations or introduce the ratio of ellipsoid axes as an additional parameter.[10,11h]

Results and Discussion

The energies of each individual tautomers of interest were calculated using eq 6 with $\epsilon = 1$ (corresponding to the gas phase, $g = 0$) and with $\epsilon = 78.4$ (water). Full geometry optimization was carried out.



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The compounds and the calculated heats of formation ΔH_F of the corresponding tautomers are listed in Table

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Table II. Calculated AM1 Dipole Moments and FMO Energies of the Tautomeric Forms of Substituted Pyridines in the Gas Phase and in an Isotropic Dielectric Medium of $\epsilon = 78.4$

	dipole moment, D		e (HOMO), eV		e (LUMO), eV	
tautomer index	$\epsilon = 1$	$\epsilon = 78.4$	$\epsilon = 1$	$\epsilon = 78.4$	$\epsilon = 1$	$\epsilon = 78.4$
I	1.723	1.947	−9.55	−9.37	0.01	0.20
II	3.926	4.903	−8.96	−8.94	−0.18	−0.15
III	1.315	1.486	−9.74	−9.69	0.04	0.08
IV	3.375	4.068	−8.30	−8.39	0.15	0.04
V	3.508	4.051	−9.76	−9.65	−0.25	−0.07
VI	5.807	7.493	−8.62	−8.79	−0.68	−0.73
VII	1.725	2.016	−9.63	−9.61	0.16	0.12
VIII	1.685	2.099	−7.61	−7.91	0.35	0.03
IX	2.981	3.520	−9.40	−9.16	0.08	0.33
X	6.227	8.259	−8.14	−8.70	−0.52	−1.00
XI	3.127	3.614	−9.74	−9.51	0.02	0.25
XII	4.399	5.727	−7.46	−7.81	−0.25	−0.55
XIII	2.927	3.446	−9.44	−9.26	−0.16	0.03
XIV	8.399	11.866	−7.83	−8.72	−0.97	−1.69
XV	2.147	2.517	−9.64	−9.46	0.14	0.31
XVI	3.605	4.662	−6.82	−7.19	−0.03	−0.33
XVII	1.954	2.307	−9.96	−9.80	0.02	0.15
XVIII	6.249	7.781	−8.94	−9.53	0.32	−0.23
XIX	2.172	2.507	−9.99	−9.85	0.06	0.21
XX	4.857	6.242	−8.25	−8.76	0.58	0.13
XXI	1.624	1.923	−9.77	−9.66	−0.09	0.01
XXII	7.943	11.600	−8.41	−9.42	−0.58	−1.54
XXIII	2.317	2.748	−9.89	−9.70	0.20	0.39
XXIV	3.002	4.114	−7.48	−7.86	−0.28	−0.32

I. All the heterocycles investigated are of approximately the same size, but small differences in the van der Waals radii of the atoms were taken into account in the calculation of the r_c values. The following values of cavity radii r_c were used: for the hydroxypyridines and pyridones, 3.15 Å; for the aminopyridines, iminopyridines, methylpyridines, and methylenepyridines, 3.25 Å; and for the mercaptopyridines and thioxopyridines, 3.40 Å. The compounds and the calculated heats of formation ΔH_F of the corresponding tautomers are listed in Table I. Dipole moments and frontier molecular orbital (FMO) energies of the molecules in the different media are presented in Table II.

No large entropy changes should occur in tautomeric equilibria comprising a single intramolecular proton transfer. Therefore, the logarithm of the tautomeric equilibrium constant should be approximately linear with the corresponding enthalpy change as in eq 9, where $\Delta S/R$

$$2.303 \log K_T = \Delta S/R + \Delta H/RT \qquad (9)$$

is presumably a small intercept. The tautomeric equilibrium constants (K_T) were calculated by eq 10, where $\delta\Delta H_F$ is the difference in the standard enthalpies of two tautomers obtained by the quantum-chemical AM1 SCF ($\epsilon = 1$) and SCRF ($\epsilon = 78.4$) methods in the two media investigated; K_T are given in Table I.

$$\log K_T(\text{calc}) = -\delta\Delta H_F/2.303RT \qquad (10)$$

Relatively few experimental data are available on the tautomeric equilibria of substituted pyridines in the vapor phase. The equilibria between 2- and 4-pyridone and corresponding hydroxypyridines, and between 2- and 4-thioxopyridine and the corresponding mercaptopyridines have been studied by Beak et al.[12,18] using gas-phase UV and IR spectroscopy, and by one of our groups using photoelectron spectroscopy and mass spectrometry data.[20] The data obtained by both groups established that, in general, the hydroxy and the mercapto tautomers are strongly favored under equilibrium conditions and show that $K_T \ll 0.1$ for most of the compounds investigated. Of the nonpyridinoid tautomers, only 2-pyridone is present in substantial amounts in the vapor phase.

The K_T value now obtained for the gas phase for 2-pyridone using the AM1 method (cf. Table I) is very close to the experimental $\log K_T = 0.4 \pm 0.3$.[18] To obtain comparable accuracy using ab initio theory requires both a large basis set and correlation energy perturbational corrections (MP2/6-31G*).[21,22] Other semiempirical and minimal basis ab initio methods have given results of doubtful value (e.g. the calculated SCF MO tautomerization energy was −15.4 kcal/mol using the STO-3G basis set,[19a] −14.2 kcal/mol by MINDO/2,[23] −3.7 kcal/mol by MINDO/3,[22] −1.7 kcal/mol using the 3-21G basis set,[22] and 11.3 kcal/mol by the CNDO/2 method). The $\log K_T$ value can be estimated approximately as 1.0 for 2-mercaptopyridine in the gas phase on the basis of PES data.[19a] Our result obtained with the AM1 parameterization ($\log K_T = 1.7$) agrees with this estimate. The indirectly measured experimental tautomerization energy for 4-hydroxypyridine (7 ± 2 kcal/mol[19a]) is also in accordance with the AM1 result (8.1 kcal/mol, cf. Table I).

Our results also agree with the experimental observation that the XH form strongly predominates in the vapor phase for the other substituted pyridines (the corresponding calculated enthalpy changes are more than 10

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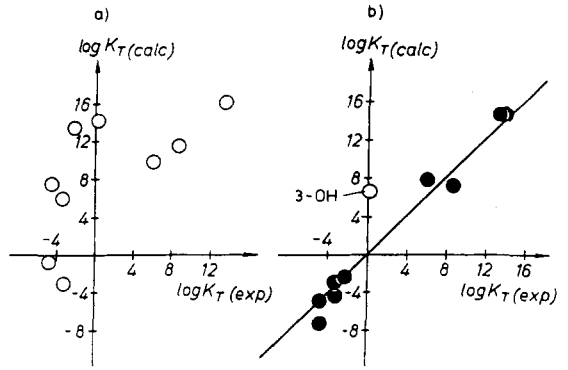

Figure 1. The relationship between the AM1 calculated and experimentally observed tautomeric equilibrium constants in solution: (a) the calculations refer to the gas phase, (b) the calculations refer to an isotropic medium with $\epsilon = 78.4$.

Table III. Calculated Relative Energies (kcal/mol) of Mono- and Dihydrates of 2-Hydroxypyridine and of 2-Pyridone

tautomer	monohydrate	dihydrate
2-hydroxypyridine	2.2	2.6 (4.5)[25]
2-pyridone	0	0

kcal/mol in favor of the XH forms; cf. the data presented in Table I). Despite the small number of the quantitative data compared, the AM1 parameterization seems to be satisfactory for the theoretical description of the intramolecular prototropic equilibria, although this conclusion needs verification with a more extensive set of experimental data.

The data presented in Table I demonstrates once more the importance of solvation effects on tautomeric equilibria. Computational results for isolated molecules can predict in several cases the wrong tautomer as dominant in solution (cf. the XH form of the 2-hydroxy-, 2-mercapto-, 3-mercapto-, 4-hydroxy-, and 4-mercaptopyridine instead of the experimentally observable oxo and thioxo forms). The results of the SCRF AM1 calculations indicate that dielectric solvation is a major, perhaps the major, factor determining the medium effect on the tautomeric equilibria of substituted pyridines. There is no correlation between the gas-phase theoretical AM1 predictions and solution experimental tautomeric equilibrium constants (cf. Figure 1a).

A plot of log K_T values calculated using the AM1 method with inclusion of the solvent reaction field for a polar solvent ($\epsilon = 78.4$) at 20 °C versus experimentally observed data in water[7] is a surprisingly good straight line with unit slope and zero intercept (Figure 1b), corresponding to eq 11 (correlation coefficient, $R = 0.988$; standard deviation, $\sigma = 0.21$).

$$\log K_T(\text{calc}) = (0.31 \pm 0.22) + (1.09 \pm 0.11) \log K_T(\text{obs}) \quad (11)$$

In strongly associated solvents, such as water, alcohols, or amides, hydrogen bonding plays an important role, and this specific interaction is not included in the reaction field model (eq 2). To investigate this point, we optimized geometries for 2-hydroxypyridine–$(H_2O)_n$ and 2-pyridone–$(H_2O)_n$ ($n = 1$ and 2). Calculated by the AM1 method, hydrogen bonds are longer (by ~0.5 Å) than those calculated by the ab initio 3-21G basis set[25] (Figure 2). The calculated energies for hydrates are summarized in Table III, and in spite of the rather long H bonds, the

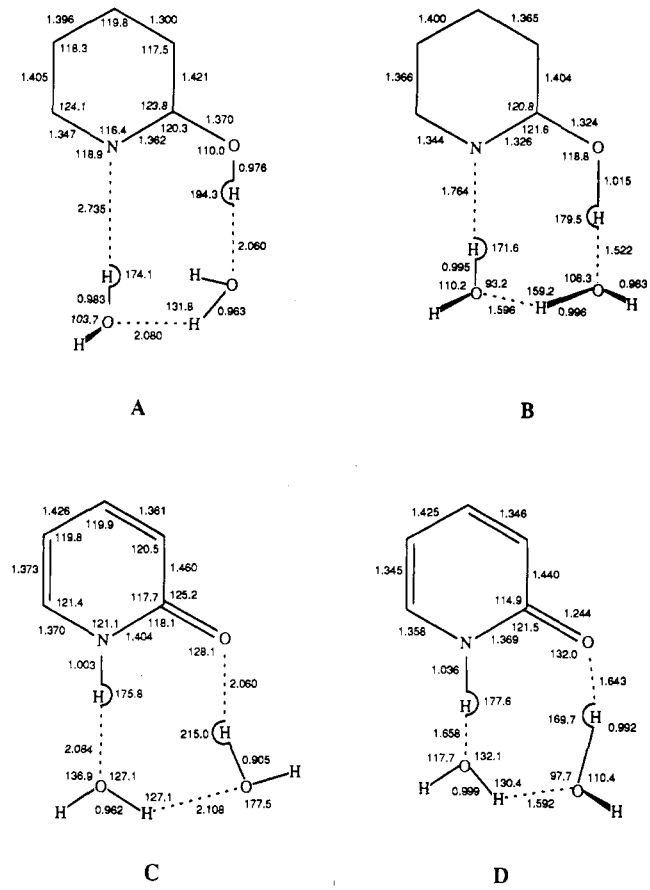

Figure 2. Calculated structures, bond lengths (Å), and angles (deg) of 2-hydroxypyridine–$2H_2O$ (A, AM1; B, 3-21G) and 2-pyridone–$2H_2O$ (C, AM1; D, 3-21G). The 3-21G data given in parentheses are taken from ref 25.

calculations predict the hydrogen-bonded lactam tautomer to be more stable that the lactim form, in good agreement with the ab initio calculation and the experimental value for 6-methoxy-2-pyridone.[12]

The Onsager classical electrostatic solvation model[11a,b] is used by some authors for the description of solvent effects on tautomeric equilibria.[12,13,19] In principle, eq 12, where m_x is the dipole moment and r_x^3 is the molecular volume of the solute x, can be applied to describe the electrostatic solvation energy term DE in expressions of tautomeric equilibrium energies.[11]

$$\text{DE} = \left(\frac{m_1^2}{r_1^3} - \frac{m_2^2}{r_2^3} \right) \frac{\epsilon - 1}{2\epsilon + 1} \quad (12)$$

Equation 12 has been applied to a variety of chemical processes either directly or in the framework of linear free energy relationships.[25-27] In both approaches, it is assumed that the dipole moment of the solute (i.e. the solute charge distribution) remains constant in different media. However, our previous SCRF calculations,[11d,e,16] and extensive experimental evidence,[28] indicate that this assumption is often unjustified.

The data presented in Table III demonstrate a significant alteration of the dipole moments of most substituted pyridine tautomers due to the solvent reaction field. The

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relative dipole moment change for different tautomers may vary considerably (e.g. m for 4-thioxopyridine increases by 46% in a medium of $\epsilon = 78.4$ when compared with $\epsilon = 1$, whereas for 4-mercaptopyridine the corresponding increase is only 18%). Such diverse variations of dipole moments invalidates the use of eq 12. When the multiplier in front of the dielectric constant function in eq 11 in LFER treatments is found empirically from the experimental data, it must be emphasized that this parameter varies with solvent. The calculated dependence of the dipole moment of the solutes on the dielectric constant function is nonlinear (cf ref 11d,e), and, moreover, the relationship between the dipole moments of the two tautomers is also not linear. Therefore, the use of eq 12 can lead only to a very qualitative description of the chemical phenomenon investigated. It follows that no "universal" single parameter solvent polarity scale[25-27,29-33] can exist for the description of chemical and physical processes.

The solvent reaction field can also have significant influence on the FMO energies of a solute molecule. However, FMO energy values for most of the structures in Table III are relatively insensitive to change in the dielectric medium. In general, the HOMO and LUMO energies of the C=X forms of tautomers are characterized by larger negative solvent shifts than those for the corresponding XH forms. For instance, the HOMO energy of 4-thioxopyridone is lowered by 1 eV and the LUMO energy of 4-pyridone by 0.55 eV, whereas the corresponding shifts for the XH forms are small positive numbers (0.1 and 0.17 eV, respectively). This observation is also reflected in the electron distributions of the molecules compared. The dipole moments of the C=X forms are altered more than those of the corresponding XH forms by the solvent reaction field. It appears that the charge redistribution in the heterocycles from the external field is due mainly to the frontier orbitals. Substantial relocalization of charge in these molecular orbitals in different dielectric media may lead to different reactivity in different dielectric media if we assume, for example, FMO theory.[34]

Several conclusions can be made on the basis of the results of the present investigation. First, our results indicate that the AM1 model[7] yields quite resonable results for the description of the prototropic equilibria, both for isolated molecules and for molecules in dielectric media (SCRF version). Secondly, the inclusion of the solvent reaction field in quantum-chemical theory is obligatory for accurate modeling of relative tautomer energies in solution. Thirdly, our results further indicate that a universal solvent polarity scale for LFER analysis is not justified. Finally, we observe that the orbitals most affected by the solvent reaction field in the substituted pyridines studied here are the frontier MO's.

Registry No. 2-Hydroxypyridine, 72762-00-6; 2(1*H*)-pyridone, 142-08-5; 2-aminopyridine, 504-29-0; 2(1*H*)-iminopyridine, 76959-52-9; 2-mercaptopyridone, 73018-10-7; 2(1*H*)-thioxopyridone, 2637-34-5; 2-methylpyridine, 109-06-8; 2(1*H*)-methylenepyridine, 34037-14-4; 3-hydroxypyridine, 109-00-2; 3(2*H*)-pyridone, 80618-81-1; 3-aminopyridine, 462-08-8; 3(2*H*)-iminopyridine, 80618-82-2; 3-mercaptopyridine, 16133-26-9; 3-(2*H*)-thioxopyridone, 76076-29-4; 3-methylpyridine, 108-99-6; 3(2*H*)-methylenepyridine, 123597-03-5; 4-hydroxypyridine, 626-64-2; 4(1*H*)-pyridone, 108-96-3; 4-aminopyridine, 504-24-5; 4-(1*H*)-iminopyridine, 29212-32-6; 4-mercaptopyridine, 4556-23-4; 4(1*H*)-thioxopyridone, 19829-29-9; 4-methylpyridine, 108-89-4; 4(1*H*)-methylenepyridine, 123597-04-6.

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Conformational Analysis of Some 1,4-Dioxepines by Molecular Mechanics (MM2)

A. Entrena,† M. A. Gallo,† A. Espinosa,*,† C. Jaime,‡ J. Campos,† and J. F. Domínguez†

Departamento de Química Orgánica, Facultad de Farmacia, Universidad de Granada, 18071 Granada, Spain, and Departamento de Química, Química Orgánica, Universidad Autónoma de Barcelona, 08193 Bellaterra, Spain

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The conformational analyses of 2,3-dihydro-5*H*-1,4-dioxepine (**5**), 5-methoxy-2,3-dihydro-5*H*-1,4-dioxepine (**6**), and 6,7-dihydro-5*H*-1,4-dioxepine (**7**) have been theoretically studied by molecular mechanics, indicating a preference for a twist-boat conformation in **5** and for a chair in **6** and **7**. The stability of the different conformations is governed by the conjugation of the oxygen atoms with the π system, in **5** and **7**, and by this conjugation and the anomeric effect in **6**. The barrier for the chair ⇌ twist boat interconversion is 2.50 kcal/mol in **5** and 3.78 kcal/mol in **6**. The concordance between calculated and experimental coupling constants of **5** and **6** upholds these results.

Introduction

The conformational analysis of seven-membered rings has been the subject of special attention in recent years, and one in which molecular mechanics has emerged as a very powerful tool. The conformational behaviors of cycloheptane,[1] 1,3-dioxepane,[2] and 1,4-dioxepane[3] have been studied with different force fields, resulting in the finding that there exists in these compounds a complex confor-

† Universidad de Granada.
‡ Universidad Autónoma de Barcelona.

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